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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,965	02/27/2004	Christopher P. Adams	3400-0009	9199

23980 7590 02/22/2006

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,965	ADAMS ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-44 are pending.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13, 15, 16, 20-23, 25, 27, 28, 30-36, and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Egan et al. (US 2002/0177586).

Egan discloses methods for treating certain fibrotic diseases or other indications, and to compounds and compositions for use in such treating (abstract and [0002]).

Egan discloses that included among the diseases treatable with his method are **arteriosclerosis, atherosclerosis, stiff vessel disease, peripheral vascular disease, coronary heart disease, stroke, myocardial infarct, cardiomyopathies, restenosis, and hypertension** [0086]-[0098].

Egan discloses that in cardiovascular therapies, first agents can be administered concurrently or in a combined formulation with one or more antioxidants. Furthermore, In treating heart failure, cardiomyopathy or heart attack, first agents can be administered concurrently or in a combined formulation with one or more **angiotensin converting enzyme**

(ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics, digitalis or **beta blockers (i.e. adrenergic inhibitors)**. Examples of calcium channel blockers include, **diltiazem, nifedipine, and verapamil** [0126-0127].

Egan discloses that the methods of his invention are used to treat animals, preferably humans [0132].

Egan discloses that pharmaceutical compositions can be prepared and can include a pharmaceutically acceptable carrier. These compositions can be prepared in a variety of forms, depending on the method of administration, including **nasal administration** [0615].

Egan discloses that the compositions can contain a **pharmaceutically acceptable carrier**, which is one or more compatible solid, or liquid filler diluents or encapsulating substances that are suitable for administration to an animal [0616]. Examples of suitable carriers include sugars (e.g. **lactose, glucose and sucrose**); cellulose and its derivatives, (e.g. **sodium carboxymethyl cellulose** and **methyl cellulose**); polyols (e.g. **propylene glycol** and **glycerine**); emulsifiers; stabilizers; antioxidants; preservatives; **pyrogen-free water**; **isotonic saline**; and **phosphate buffer solutions** [0617]. The Applicant has generically identified alcohols as examples of permeation enhancers on page 17, [0062] of the specification. Propylene glycol and glycerine are alcohols and are inherently permeation enhancers, per Applicant's admission. The Applicant has also identified sodium carboxymethyl cellulose and methylcellulose as examples of bioadhesive materials on page 17 of the specification, [0061].

Egan discloses that compositions intended for nasal administration preferably comprise from **about 0.01% to about 10.0% w/v of a subject compound**. Similar compositions are preferred for **systemic delivery of subject compounds** by the **intranasal route**. Compositions

used for intranasal dosing also typically include safe and effective amounts of preservatives; chelating agents; buffers; tonicity agents (e.g. **glycerin and mannitol**); antioxidants; aromatic agents; viscosity adjustors (e.g. cellulose and derivatives); polyvinyl alcohol; local anesthetics or **other actives**, and acids and bases. These compositions can be used as **sprays**, etc [0622].

Other preferred compositions of this invention include **aqueous solutions, suspensions, and dry powders** comprising an effective amount of a subject compound intended for **atomization and inhalation** administration. Such compositions are typically contained in a container with attached atomizing means. Such compositions also typically include **propellants** (e.g. chlorofluorocarbons and fluorocarbons) or other nontoxic volatiles; solvents such as water, **glycerol and ethanol**, including cosolvents; stabilizers; preservatives, etc. [0623]. The Applicant has generically identified alcohols as examples of permeation enhancers on page 17, [0062] of the specification. Ethanol and glycerol are alcohols and thus, are inherently permeation enhancers, per Applicant's admission.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 5-13, 15, 16, 20-36 and 40-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Krause (US 2004/0014782).

Krause discloses compositions and methods for treating diseases that are associated with inflammation are provided, including arthritis and other autoimmune disorders, asthma, cardio- and cerebrovascular disease, burns, psoriasis, reperfusion injury, and traumatic CNS and spinal

cord injury. The compositions generally comprise **at least one C5a antagonist** and **at least one C5a receptor-inactive therapeutic agent** (abstract).

Krause discloses that a wide variety of diseases and medical procedures can result in harmful inflammation, and inhibition of C5a-mediated inflammatory responses in patients afflicted with diseases or undergoing procedures that are associated with inflammation including, for example, diseases of the joints, lungs, kidneys, **heart,** skin, liver, and digestive system, and as well as more generally, trauma and auto-immune and infectious diseases [0005]. Regarding cardio- and cerebrovascular diseases, Krause discloses that low-level inflammation has been correlated to the incidence of heart attack and stroke [0021] and [0022].

Krause's invention discloses pharmaceutical compositions, comprising a C5a antagonist in combination with a C5a receptor-inactive therapeutic agent and a pharmaceutically acceptable **carrier or excipient**. Pharmaceutical formulations, such as tablets, pills and capsules, containing a C5a antagonist and a C5a receptor-inactive therapeutic agent are included in the invention. Pharmaceutical formulations may include **additional active or inert ingredients** [0030].

Krause discloses **methods for treating a patient suffering from disorders, including cardio- or cerebrovascular diseases**, comprising **administering** to the patient a therapeutically effective amount of a C5a receptor antagonist **in combination** with a therapeutically effective amount of a C5a receptor-inactive therapeutic agent. This therapy encompasses either or both of 1) the administration of a C5a antagonist and a C5a receptor-inactive therapeutic agent together, and 2) the administration of a C5a antagonist in a first formulation and the separate administration of a C5a receptor-inactive therapeutic agent in a second pharmaceutical formulation [0032].

Krause discloses that administration may be oral, **intranasal**, topical, rectal or parenteral [0038].

Krause discloses that the pharmaceutical compositions of his invention may be administered to "patient at risk for myocardial infarction or stroke"; meaning patients with known risk factors for myocardial infarction and stroke including such risk factors as, **hypertension** [0081] and claim 31.

Krause discloses that the C5a receptor antagonist in combination with a therapeutically effective amount of a C5a receptor-inactive therapeutic agent, including, **calcium channel blockers, diuretics adrenergic receptor agonists, alpha/beta adrenergic receptor antagonists, beta adrenergic receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and peripheral vasodilators** [0244]. Examples of suitable calcium channel blockers include **diltiazem hydrochloride** (CARDIZEM®) and **nifedipine** (ADALAT®, PROCARDIA®, PROCARDIA®) [0254].

Krause discloses that the C5a receptor-inactive therapeutic agent is an **anti-hypertensive agent** [0248], including **angiotensin converting enzyme (ACE) inhibitor**. Suitable angiotensin converting enzyme (ACE) inhibitors are listed in paragraph [0251]. See also claim 21.

Krause discloses that in certain particularly preferred embodiments, the combination administration of **at least one C5a receptor antagonist with at least one C5a receptor-inactive therapeutic agent** results in a reduction of the dosage of the C5a receptor-inactive therapeutic agent required to produce a therapeutic effect [0265].

Krause discloses that the dosage regimen utilizing a C5a antagonist and a C5a receptor-inactive therapeutic agent is selected in accordance with a variety of factors including species,

age, weight, sex, medical condition of the patient, and other pharmaceutical agents that are being administered to the patient during treatment in accordance with the present invention. These factors further include the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compounds (including any salts or prodrugs thereof) employed [0272].

Krause discloses that inhalation formulations may be delivered via any inhalation methods known to those skilled in the art. Such inhalation methods and devices include, but are not limited to, **metered dose inhalers with propellants** such as **CFC or HFA or propellants** that are physiologically and environmentally acceptable. Other included devices are breath-operated inhalers, **multidose dry powder inhalers and aerosol nebulizers** [0298]. Formulations may include **powder or aerosol carriers**. The inhalant compositions used in the present invention may comprise **liquid or powdered compositions containing the active ingredient** that are suitable for nebulization and intrabronchial use, or aerosol compositions administered via an **aerosol unit dispensing metered doses** [0299]. Suitable **liquid compositions** comprise the active ingredient in an **aqueous**, pharmaceutically acceptable inhalant solvent, e.g., **isotonic saline** or b**acteriostatic water**, administered by means of **a pump or squeeze-actuated nebulized spray dispenser** [0300]. Suitable **powder compositions** include powdered preparations of the active ingredient intermixed with **lactose** or other inert powders, administered via an **aerosol dispenser** or encased in a breakable capsule which may be inserted by the patient into a device that punctures the capsule and blows the powder out in a steady stream suitable for inhalation [0301]. Aerosol formulations for use in the subject method would typically include propellants, surfactants and co-solvents and may be filled into

conventional aerosol containers [0302]. Formulations for nasal administration, utilizing a solid carrier, include a coarse powder having a particle size ranging from 20 to 500 microns, administered in the manner in which snuff is administered, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations with a **liquid carrier** may be administered as a **nasal spray or as nasal drops**, including as aqueous or oily solutions of the active ingredient [303]. Aqueous suspensions contain the active materials in admixture with excipients, including suspending agents (e.g. **sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone**), one or more preservatives, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents (e.g. **sucrose**) [0292]. The suspending agents disclosed by Krause include compounds the Applicant has identified as bioadhesive materials. Therefore, sodium carboxymethylcellulose, methylcellulose, hydropropyl methylcellulose, sodium alginate, and polyvinylpyrrolidone are inherently bioadhesive materials.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil. The oily suspensions may contain a thickening agent, including **cetyl alcohol** [0293]. The Applicant has generically identified alcohols as examples of permeation enhancers on page 17, [0062] of the specification. Therefore, cetyl alcohol is inherently a permeation enhancer.

Krause's methods inherently encompass the methods described in claims 24-25 of the instant application, because they have the same step of administering a calcium channel blocker intranassally. Because Krause's methods inherently encompass those state in claims 24-25 of the instant application, these methods must also inherently have the properties stated in said claims, namely, targeting delivery of a calcium channel blocker to the brain, maximizing the amount of

calcium channel blocker reaching the brain, and minimizing peripherally mediated adverse events.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 4, 14, 17-19, 37-39, and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krause (US 2004/0014782) in view of Wermeling et al. (WO 02/13886).

The disclosures/teachings of Krause have been set forth above.

Additional relevant teachings of Krause are set forth below.

Krause teaches in Example 9E oral suspensions comprising C5a antagonist (5-100 mg), C5a receptor inactive therapeutic agent (5-100 mg), polyvinylpyrrolidone (150 mg), polyoxyethylene sorbitan monolaurate (25 mg; 10 mg to 5 mL with sorbitol solution), and benzoic acid (70%). The range in the amount of C5a receptor inactive therapeutic agent represents an amount ranging from about 0.8% to 8.0% w/w.

Krause teaches topical formulations **controlled release vehicles** can also be used to administer the pharmaceutical formulations of his invention and these include **methylcellulose, polyvinylpyrrolidone, carboxymethylcellulose**, etc. Krause teaches that the technology and products in this art are variably referred to as **controlled release**, **sustained release**, prolonged action, depot, repository, delayed action, retarded release and **timed release**; the words "controlled release" incorporates each of the foregoing technologies. Controlled release drug delivery devices include gels, microspheres, liposomes, etc. These preparations can be achieved by the use of polymers to complex or absorb the active agent(s), selecting the appropriate macromolecules, the concentration of these macromolecules, and the methods of incorporation. For example, it is known in the art that hydrogels, wherein the active agent(s) are dissolved in an aqueous constituent; and matrix devices, wherein the active agent(s) are dispersed in a matrix of carrier material may be used to gradually release over time. Alternatively, a device comprising a

central reservoir of active agent(s) surrounded by a rate controlling membrane can be used to control the release of active agent(s) [0309]-[0311].

Krause lacks the explicit teaching of devices capable of delivering unit dosages of a given active agent via intranasal administration.

Wermeling teaches programmable multi-dose **intranasal drug delivery devices** for the self-administration of a plurality of doses of an intranasal **liquid pharmaceutical composition**, that includes a drug delivery device containing a plurality of sealed vials, **each vial containing a predetermined volume (i.e. dosage) of the pharmaceutical composition**, a pump assembly for conveying the liquid composition and discharging it as a **nasal spray** (abstract and title).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Krause and Wermeling, because Krause teaches compositions that can be administered intranassally and Wermeling teaches intranasal drug delivery devices. A skilled artisan would have been motivated to combine the teachings of Krause and Wermeling to administer Krause's intranasal formulations using Wermeling's intranasal drug delivery devices. Because Wermeling's devices were designed to deliver compositions intranassally, a person of ordinary skill in the art would have had a reasonable expectation of success upon combination of the prior art teachings.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention that the dosage amount of a drug or drugs in a formulation can be modified in the course of optimization from one form of administration (e.g. oral) to another (e.g. nasal). Furthermore, Krause teaches that the amounts of actives may be modified by skilled artisans to amounts appropriate for different routes of administration and according to the medical condition

and physical characteristics of the patient receiving treatment (see Krause, [0272]). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Likewise, it would have been obvious to a skilled artisan that one could modify a formulation for nasal administration to have controlled release properties, because the materials and methods required to obtain a controlled release formulation are well known in the art (see Krause, [0309]-[0311]). Regarding 43-44, devices for delivering pharmaceutical compositions housed within said devices are well known in the art (Wermeling) and Krause also teaches that suitable devices include metered-dose inhalers, dry powder inhalers, aerosol spray nebulizers, etc (see [0299]-[0303]).

Double Patenting

Applicant is advised that should claims 17 and 37 be found allowable, claims 18-19 and 38-39 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The

term "timed release" is used interchangeably in the art with the terms "controlled release" and "sustained release." See for example, [309] in Krause (US 2004/0014782).

Conclusion

Claims 1-44 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Examiner

SUPERVISORY PATENT EXAMINER